Impact of Precision Medicine in Diverse Cancers: a Meta-Analysis of 32,149 Patients in Phase II Clinical Trials

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Details of study selection and Data Extraction:

We considered response rate (RR), progression free survival (PFS) or time to progression (TTP) when PFS was not available, and overall survival (OS) as acceptable efficacy endpoints.

The following information were extracted from manuscripts: five-years impact factor, underlying malignancy, line of therapy, class of agent, route of administration, presence and type of biomarker used for patient selection, number of enrolled patients, description of arms (if applicable), drug dose/schedule, response criteria adopted, median PFS and 95%CI (or TTP when PFS not available), median OS and 95%CI, and RR (%), number of responders, and treatment related deaths.

Responses were recorded according to the response criteria utilized in the trial: for solid tumors, partial and complete responses as per Response Evaluation in Solid Tumors Criteria (RECIST) or World Health Organization Criteria (WHO); for chronic myelogenous leukemia (CML), complete cytogenetic responses; for multiple myeloma (MM), partial and complete responses; for acute myelogenous leukemia (AML), complete responses; and for lymphomas, partial and complete responses by WHO criteria.

Personalized therapy definition:

For the purpose of our analysis we defined personalized therapy when a treatment met one of the following criteria: i. Cognate biomarker used for treatment indication OR ii. No cognate biomarker used, but at least 50% of patients are known to harbor the cognate biomarker (e.g. patients with gastro-intestinal stromal tumors (GIST; drug targeting KIT); chronic myeloid leukemia (CML; drug targeting BCR-Abl); or chronic lymphocytic leukemia (CLL; drug targeting CD-20)).

A drug was considered personalized if the half maximal inhibitory concentration (IC_{50}) impacted the target at low nM range (<100 nM) (for small molecule inhibitors) or if the target was the primary one recognized by an antibody. (Targeted arms that did not select patients according to our definition of a personalized strategy (see above) were considered non-personalized.) More specifically, we defined "personalized–direct" as a drug that directly impacts the product of the molecular alteration or a protein preferentially expressed on the tumor cells, or its first immediate downstream effectors. Examples would include a PIK3CA inhibitor in a patient with either a *PIK3CA* mutation (direct effect on the molecular aberration) or *PTEN* loss (effect on first downstream effectors' since *PTEN* loss results in PIK3CA activation). "Personalized–indirect" was the term used for a drug that affects a target at least two effectors removed from the molecular aberration. Examples would include an mTOR inhibitor in a patient with a *PIK3CA* mutation (since PIK3CA signals through AKT to mTOR) or in a patient with *PTEN* loss (which activates PIK3CA, which then in turn activates AKT and mTOR). We also included in "personalized indirect" small molecule inhibitors that had an IC50 over 100nM; but no more than 250nM, even if the target affected was the direct cognate or only one step removed.

The complexity of signal cascades suggests that many signals intersect at some point. Molecular aberrations are likely to activate several interacting pathways and, hence, a drug impacting an effector far removed from the aberration would be less likely to mitigate the effect of the aberration and was considered "not personalized". Complicating this classification is the possibility that pathways have multiple intermediaries that might be differentially activated depending on tumor histology. Therefore, therapies that targeted pathways further removed from the aberration were not considered personalized.

Definition of cytotoxic versus targeted agent:

Cytotoxic chemotherapy uses chemical substances to kill cells that divide rapidly (a key feature of cancer cells). That means that cytotoxics also harm normal, rapidly dividing cells, such as those in the bone marrow, gastrointestinal tract and hair follicles, often resulting in myelosuppression, mucositis and alopecia. Targeted agents are frequently cytostatic and are designed to specifically impact signals in the cancer cell that are abnormal or are differentially expressed compared to those on normal elements. In our analysis, immunotherapies were classified as targeted.

Supplemental Table 1. Sub-analysis of personalized arms for the response rate (RR), progression-free survival (PFS), and overall survival (OS) –univariable analysis–

		Pooled analysis			Meta-analysis		
		N	*Median (CI 95%)*	*P-value*[a]	*N*	*Median (CI 95%)*	*P-value*[b]
RESPONSE RATE (RR) (%)	Total arms with valid values for RR	**638**	8 (6.8-8.9)		**638**	12.7 (11.6-13.9)	
	Personalized TOTAL			**<0.0001**			**<0.0001**
	Yes	112	29.2 (24-35)		112	31 (26.8-35.6)	
	Not personalized	526	6.2 (5-7.4)		526	10.5 (9.6-1.5)	
	Personalized DIRECT[c]			**<0.0001**			**<0.0001**
	Yes	82	27.7 (23.7-36.0)		82	32.3 (27.1-38.1)	
	Not personalized	526	6.2 (5-7.4)		526	10.5 (9.6-1.5)	
	Personalized INDIRECT			**<0.0001**			**<0.0001**
	Yes	30	30.5 (15.8-35.3)		30	29.5 (24.2-35.4)	
	Not personalized	526	6.2 (5-7.4)		526	10.5 (9.6-1.5)	
PROGRESSION-FREE SURVIVAL (PFS) (Median, Months)	Total arms with valid values for PFS	**530**	3 (2.8-3.2)		**342**	3 (2.9-3.1)	
	Personalized TOTAL			**<0.0001**			**<0.0001**
	Yes	86	6.8 (5.3-7.6)		59	5.9 (5.4-6.3)	
	Not personalized	444	2.8 (2.7-3.0)		283	2.7 (2.6-2.9)	
	Personalized DIRECT[c]			**<0.0001**			**<0.0001**
	Yes	59	5.6 (4-7.7)		39	5.8 (5.2-6.4)	
	Not personalized	444	2.8 (2.7-3.0)		283	2.7 (2.6-2.9)	
	Personalized INDIRECT			**<0.0001**			**<0.0001**
	Yes	27	7.4 (6.4-8.4)		20	6.4 (5.3-7.5)	
	Not personalized	444	2.8 (2.7-3.0)		283	2.7 (2.6-2.9)	
OVERALL SURVIVAL (OS) (Median, Months)	Total arms with valid values for OS	**441**	9.4 (8.8-10.0)		**247**	9.1 (8.6-9.6)	
	Personalized TOTAL			**<0.0001**			**0.0003**
	Yes	49	15.9 (11.4-18.3)		21	13.7 (11.1-16.4)	
	Not personalized	392	9 (8.3-9.7)		226	8.9 (8.3-9.3)	
	Personalized DIRECT[c]			**0.001**			**<0.0001**
	Yes	38	15.4 (11-18)		17	12.6 (9.9-15.3)	
	Not personalized	392	9 (8.3-9.7)		226	8.9 (8.3-9.3)	
	Personalized INDIRECT			**0.001**			**<0.0001**
	Yes	11	23.1 (10.3-32.5)		4	19.2 (13.3-25)	
	Not personalized	392	9 (8.3-9.7)		226	8.9 (8.3-9.3)	

[a]Wilcoxon test ; [b]Mixed effect analysis. [c]"personalized direct" was defined as a drug that directly impacts the product of the molecular alteration or a protein preferentially expressed on the tumor cells, or its first immediate downstream effectors. If "personalized direct" was defined as as a drug that strictly impacts directly the product of the molecular alteration or a protein preferentially expressed on the tumor cells (not its first immediate downstream effector), results were also statistically significant for all the analysis, except the overall survival analysis in the meta-analysis, though numbers were very low (data not shown). CI means confidence interval.

Supplemental Table 2. Sub-analysis of the type of biomarker used for personalized arms (univariable analysis)

		Pooled analysis			Meta-analysis		
		N	*Median (CI 95%)*	*P-value*[a]	*N*	*Median (CI 95%)*	*P-value*[b]
RR (%)	**Total arms with RR reported**	**112**	29.2 (24-35)		**112**	31 (26.8-35.6)	
	Type of biomarker used			**0.005**			**0.027**
	Protein	34	18.7 (6.4-28.5)		34	24.2 (18.5-31.0)	
	Genomic	78	33.3 (26.3-41.0)		78	34.1 (28.6-40.1)	
PFS (Months)	**Total arms with PFS reported**	**86**	6.8 (5.3-7.6)		**59**	5.9 (5.4-6.3)	
	Type of biomarker used			**0.005**			**0.015**
	Protein	24	3.7 (1.8-6.4)		15	5.0 (4.3-5.8)	
	Genomic	62	7.5 (6.4-9.0)		44	6.4 (5.6-7.1)	
OS (Months)	**Total arms with OS reported**	**49**	15.9 (11.4-18.3)		**21**	13.7 (11.1-16.4)	
	Type of biomarker used			**<0.0001**			**0.007**
	Protein	15	6.0 (5.3-11.0)		5	8.2 (3.6-12.8)	
	Genomic	34	18.6 (15.9-24.3)		16	16.0 (12.7-19.2)	

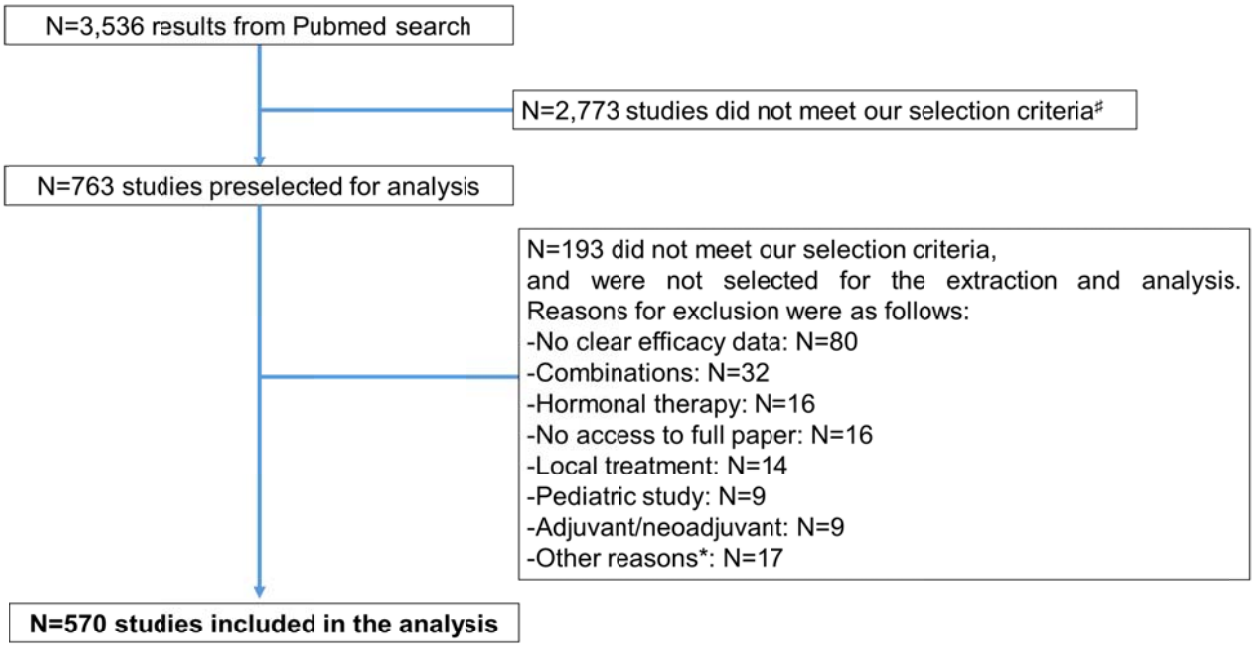
[a]Wilcoxon test ; [b]Mixed effect analysis. A “protein biomarker” was defined as the presence of a protein overexpression (included Bcl-2, CD20, CD33, CD4, CD52, c-Kit, ERCC, PDGFR, EGFR, EpCAM, HER2, NOTCH, PSCA, and RANKL); “genomic biomarker” was defined as the presence of a genetic alteration (included BCR-ABL, BRAF, BRCA1/2, EGFR, ERBB2, FLT3, JAK2, KIT, KRAS, PDGFB, PTEN, RET, TSC1/2, or VHL alterations). Abbreviations: RR: Response rate; PFS: Progression-free survival; OS: Overall survival; CI: confidence interval.

Supplemental Table 3. Sub-analysis of the outcome parameters in targeted and cytotoxic arms.

		Pooled analysis			Meta-analysis		
		N	*Median (CI 95%)*	*P-value*[a]	*N*	*Median (CI 95%)*	*P-value*[b]
RR (%)	**Total arms with RR reported for sub-analysis**	**426**			**426**		
	Targeted personalized	111	30 (24-34.8)	<0.0001	111	31.3 (27-36)	<0.0001
	Targeted non-personalized	315	4 (3-5)		315	7.5 (6.6-8.5)	
	Total arms with RR reported for sub-analysis	**323**			**323**		
	Targeted personalized	111	30 (24-34.8)	<0.0001	111	31.3 (27-36)	<0.0001
	Cytotoxic	212	11.9 (9.3-14.5)		212	16.1 (14.3-18)	
	Total arms with RR reported for sub-analysis	**527**			**527**		
	Targeted non-personalized	315	4 (3-5)	<0.0001	315	7.5 (6.6-8.5)	<0.0001
	Cytotoxic	212	11.9 (9.3-14.5)		212	16.1 (14.3-18)	
PFS (Months)	**Total arms with PFS reported for sub-analysis**	**355**			**233**		
	Targeted personalized	85	6.9 (5.3-7.7)	<0.0001	58	6.1 (5.6-6.6)	<0.0001
	Targeted non-personalized	270	2.6 (2.3-2.8)		175	2.5 (2.4-2.6)	
	Total arms with PFS reported for sub-analysis	**260**			**167**		
	Targeted personalized	85	6.9 (5.3-7.7)	<0.0001	58	6.1 (5.6-6.6)	<0.0001
	Cytotoxic	175	3.3 (3.0-3.7)		109	3.3 (3.0-3.5)	
	Total arms with PFS reported for sub-analysis	**445**			**284**		
	Targeted non-personalized	270	2.6 (2.3-2.8)	<0.0001	175	2.5 (2.4-2.6)	<0.0001
	Cytotoxic	175	3.3 (3.0-3.7)		109	3.3 (3.0-3.5)	
OS (Months)	**Total arms with OS reported for sub-analysis**	**274**			**148**		
	Targeted personalized	48	15.9 (13.5-18.3)	<0.0001	21	13.7 (11-16.4)	<0.0001
	Targeted non-personalized	226	8.7 (7.9-9.5)		127	8.3 (7.7-8.9)	
	Total arms with OS reported for sub-analysis	**215**			**120**		
	Targeted personalized	48	15.9 (13.5-18.3)	<0.0001	21	13.7 (11-16.4)	0.002
	Cytotoxic	167	9.4 (8.5-10.4)		99	9.3 (8.5-10.1)	
	Total arms with OS reported for sub-analysis	**393**			**226**		
	Targeted non-personalized	226	8.7 (7.9-9.5)	0.054	127	8.3 (7.7-8.9)	0.048
	Cytotoxic	167	9.4 (8.5-10.4)		99	9.3 (8.5-10.1)	

[a]Wilcoxon test ; [b]Mixed effect analysis. Abbreviations: RR: Response rate; PFS: Progression-free survival; OS: Overall survival; CI: confidence interval. Only one arm was personalized in the "cytotoxic".

Supplemental Figure 1. Flow diagram of studies inclusion/exclusion



#Reading of the study title clearly mentioned an exclusion criteria; main reasons were combinations, hormonal therapy, pediatric study or local treatment were tested.
*Other reasons for exclusion: cell and vaccine therapy, n=9; update on study initially published outsice of the selection timeframe, n=3; Not a phase II study, n=3; Regimen comprised radiotherapy, n=2.

Supplemental Reference List (N=570 studies included)

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